

Inspicos A/S

Bøge Allé 3

P.O. Box 45

DK-2970 Hørsholm

CVR 27 05 89 22

27 SEP. 2004

From the INTERNATIONAL SEARCHING AUTHORITY

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:

INSPICOS A/S

Bøge Allé 3

P.O. Box 45

DK-2970 Hørsholm

DENMARK

(PCT Rule 44.1)

Date of mailing
(day/month/year)

28/09/2004

Applicant's or agent's file reference

15685PCT00

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/DK2004/000001

International filing date
(day/month/year)

07/01/2004

Applicant

SYMPHOGEN A/S

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

Anna Rauf

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15685PCT00	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/DK2004/000001	International filing date (day/month/year) 07/01/2004	(Earliest) Priority Date (day/month/year) 07/01/2003
Applicant SYMPHOGEN A/S		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).**3. ☐ Unity of invention is lacking (see Box III).****4. With regard to the title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 3

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK2004/000001

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000001

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/10 C12N5/10 C12N15/85 C12N15/64 C07K16/00 C07K14/705 A61K39/395 A61K38/17		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/055718 A (HUA SHAOBING BENJAMIN ; LIN YU-HUEI (US); GENETASTIX CORP (US); SHERID) 18 July 2002 (2002-07-18)	41,42
Y	page 7, line 19 - line 24 page 17, line 28 - page 18, line 22 page 21, line 8 - line 25 page 64, line 23 - page 66, line 13	1-40
Y	WO 02/44361 A (HUSE WILLIAM D ; APPLIED MOLECULAR EVOLUTION IN (US)) 6 June 2002 (2002-06-06) page 10, line 15 - line 32 page 16, line 4 - page 18, line 15 page 32, line 16 - page 33, line 24 page 42, line 25 - line 30 claims 1-40	1-40
	----- -/--	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 14 September 2004		Date of mailing of the international search report 28/09/2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Mandl, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK2004/000001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 789 208 A (SHARON JACQUELINE) 4 August 1998 (1998-08-04) abstract column 17, line 21 - line 64 column 18, line 29 - line 34 -----	41-47
X	WO 01/89563 A (SYMPHOGEN AS) 29 November 2001 (2001-11-29) abstract; claims 1-24 -----	41,43, 45,46
A	US 5 677 177 A (WAHL GEOFFREY M ET AL) 14 October 1997 (1997-10-14) cited in the application abstract claims 1-24 -----	1-40
A	WO 00/11155 A (UNIV LELAND STANFORD JUNIOR) 2 March 2000 (2000-03-02) abstract; claims 1-71 -----	1-47
A	SODERLIND E ET AL: "Recombining germline-derived CDR sequences for creating diverse single-framework antibody libraries" NATURE BIOTECHNOLOGY, vol. 18, no. 8, August 2000 (2000-08), pages 852-856, XP002242392 ISSN: 1087-0156 cited in the application the whole document -----	1-47
A	WO 98/41645 A (IDEC PHARMA CORP) 24 September 1998 (1998-09-24) cited in the application the whole document -----	1-47

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 43 and 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK2004/000001

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02055718	A	18-07-2002	US 6610472 B1 WO 02055718 A2 US 2003219817 A1	26-08-2003 18-07-2002 27-11-2003
WO 0244361	A	06-06-2002	AU 3936902 A CA 2430080 A1 EP 1337631 A2 JP 2004514444 T WO 0244361 A2 US 2004087014 A1	11-06-2002 06-06-2002 27-08-2003 20-05-2004 06-06-2002 06-05-2004
US 5789208	A	04-08-1998	US 6335163 B1 US 2001049107 A1 AT 243745 T AU 1736495 A DE 69531148 D1 DE 69531148 T2 DK 744958 T3 EP 1231268 A2 EP 0744958 A1 ES 2201097 T3 PT 744958 T WO 9520401 A1	01-01-2002 06-12-2001 15-07-2003 15-08-1995 31-07-2003 29-04-2004 20-10-2003 14-08-2002 04-12-1996 16-03-2004 28-11-2003 03-08-1995
WO 0189563	A	29-11-2001	AU 6206701 A CA 2410586 A1 CN 1437482 T WO 0189563 A1 EP 1283720 A1 JP 2003534290 T US 2002009453 A1	03-12-2001 29-11-2001 20-08-2003 29-11-2001 19-02-2003 18-11-2003 24-01-2002
US 5677177	A	14-10-1997	US 2002166138 A1 US 5654182 A US 5885836 A WO 9215694 A1	07-11-2002 05-08-1997 23-03-1999 17-09-1992
WO 0011155	A	02-03-2000	AU 5898599 A WO 0011155 A1 US 2003050258 A1	14-03-2000 02-03-2000 13-03-2003
WO 9841645	A	24-09-1998	US 5830698 A US 5998144 A AU 737155 B2 AU 6443598 A BR 9808584 A CA 2283740 A1 CN 1255166 T CZ 9903162 A3 EP 0981637 A1 ID 24565 A JP 2001516221 T NO 994397 A NZ 337676 A PL 335695 A1 WO 9841645 A1 US 2002192820 A1 US 6413777 B1	03-11-1998 07-12-1999 09-08-2001 12-10-1998 23-05-2000 24-09-1998 31-05-2000 16-02-2000 01-03-2000 27-07-2000 25-09-2001 09-11-1999 26-01-2001 08-05-2000 24-09-1998 19-12-2002 02-07-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK2004/000001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9841645	A	US 2004166528 A1	26-08-2004
		ZA 9802152 A	09-10-1998
		HU 0002320 A2	28-11-2000

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/DK2004/000001

International filing date (day/month/year)
07.01.2004

Priority date (day/month/year)
07.01.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/10, C12N5/10, C12N15/85, C12N15/64, C07K16/00, C07K14/705, A61K39/395, A61K38/17

Applicant
SYMPHOGEN AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Mandl, B

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/DK2004/000001

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/DK2004/000001

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/DK2004/000001

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 43 and 44 with regard to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 43 and 44 with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/DK2004/000001

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-40
	No: Claims	41-47
Inventive step (IS)	Yes: Claims	
	No: Claims	1-47
Industrial applicability (IA)	Yes: Claims	1-42,45-47
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 43 and 44 relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv) PCT**. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (**Article 34(4)(a)(I) PCT**).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/055718 (GENETASTIX CORP); 18 July 2002

D2: WO 02/44361 (APPLIED MOLECULAR EVOLUTION INC.); 6 June 2002

D3: US-A-5 789 208 (SHARON JACQUELINE); 4 August 1998

1) The subject-matter of claims 41-47 is not novel (**Article 33(2) PCT**) for the following reasons:

i) The subject-matter of claims 41-47 relates to products being defined in terms of a process for their preparation (product-by-process' claims). A product, however, is not rendered novel merely because a new process for its production has been used.

ii) Recombinant polyclonal antibodies, T-cell receptors and fragments thereof as well as their use in pharmaceutical compositions for the treatment of all types of diseases including cancer and infections have already been disclosed in **D3** (col. 17, l. 21-64; col. 18, l. 29-34). Thus, the disclosures made by **D3** anticipate the novelty of claims 41-47.

2) The subject-matter of claims 1-40 does not involve an inventive step (**Article 33(3) PCT**) for the following reasons:

i) Document **D1** is regarded as being the closest prior art to the subject-matter of claims 1, 32 and 37. **D1** discloses a method for generating a collection of cells suitable for the manufacture of a protein library of polyclonal proteins, like antibodies and TCRs, by introduction of a library of corresponding vectors encoding each one distinct member of the polyclonal proteins.

ii) The subject-matter of claims 1, 32 and 37 differs from the method disclosed in **D1** in that the nucleic acids encoding the members of the polyclonal proteins are integrated into the cellular genome at an identical site by site-directed recombination via recombinase recognition sequences.

iii) The problem to be solved by the present invention may be regarded as the improvement of the method of **D1** with regard to production efficiency and minimal batch variations.

iv) The solution proposed in claims 1, 32 and 37 of the present application, i.e. the integration of the coding nucleic acid sequences into the genome of the producer cells by site-directed recombination, cannot be considered as involving an inventive step because **D1** has already pointed at the possibility of integration of the distinct nucleic acids into the genome of the producer cells (**D1**: p.85, l.7-9) hereby giving an incentive to look for appropriate integration systems.

v) Consequently, the invention of claims 1, 32 and 37 consists merely of the execution of the proposal given by **D1**, and is characterized by the use of standard technology which has already been used in the context of the expression of polyclonal proteins (antibodies, TCRs, etc.) in a cell line of isogenic cells (see **D2**: p.16, l.14 - p.18, l.15; p.42, l.25.30). **D2** specifically stresses the high accuracy of the system which minimizes clonal variation. Consequently, from the disclosures made by **D2**, the skilled person did not only know how the site-specific recombination should be done but also that it resulted in clone stability which directly implied batch stability and, consequently, higher production rates.

The Examining Division is, therefore, of the opinion that the skilled person, without the exercise of inventive skills would have employed the cloning system described for polyclonal proteins in **D2** to improve the method of **D1** with a reasonable expectation of success.

vi) Dependent claims 2-31, 33-36 and 38-40 do not contain any features which, in

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/DK2004/000001

combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step because the various features referred to in said claims were all well known from documents **D1** and **D2**.